IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Gill et al.
Application No.	:	10/069,691
Filing Date	:	June 3, 2002
Art Unit	:	1618
Title	:	Improved Container Composition for Radiopharmaceutical Agents
Docket No.	:	PZ9947 US

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Commissioner for Patents
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APPEAL BRIEF

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I. REAL PARTY IN INTEREST

The real party in interest in this Appeal is GE Healthcare Limited (now part of General Electric "GE").

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF CLAIMS

Claims 1-14 are pending in this application. The Examiner has rejected all of these claims. Claims 1-14 as amended during prosecution are reproduced in the claims appendix attached hereto. Appellants are appealing the rejections of Claims 1-14.

IV. STATUS OF AMENDMENTS

Appellants filed a Response with claim amendments on September 28, 2007 and Appellants received a final Office Action on December 12, 2007. No claims were amended subsequent to the Examiner's final rejection that was mailed on December 12, 2007.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent Claim 1 describes a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface wherein the improvement being that the radiopharmaceutical comprises a coordination complex of a metal with an organic ligand.

Support for claim 1 can be found on page 3, line 21 to page 6 of the specification.

Independent Claim 6 describes a kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface.

Support for claim 6 can be found on page 8, line 16 of the specification.

Independent Claim 10 describes a composition for the preparation of a stabilized radiopharmaceutical metal complex which comprises a stabilizer capable of stabilizing said radiopharmaceutical metal complex and an organic ligand which forms a coordination complex with the meta; in a container which has a silica coating on the inner surface.

Support for claim 10 can be found on page 3 to page 7 of the specification.

Independent Claim 11 describes a composition for the preparation of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.

Support for claim 11 can be found on page 3 to page 7 of the specification.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues for review in this appeal arise from a Final Rejection that was mailed on December 12, 2007. The Examiner rejected claims 1-14 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,961,952 ("Crane") in view of JP 11-99192 ("Yamaguchi") in further view of DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther").

Therefore, the issues in this appeal are:

1. Whether Crane in view of Yamaguchi and in further view of Schott Glaswerke, or Walther disclose or suggest all the elements of claims 1-14?

2. Whether Crane in view of Yamaguchi and in further view of Schott Glaswerke or Walther contain a motivation to combine one reference with the other reference?

VII. GROUPINGS OF CLAIMS

In accordance with 37 CFR 1.192(c)(7), the Appellants state that the four separately grouped claims 1-5, 6-9, 10, and 11-14 do not stand or fall together.

VIII. ARGUMENT

The Examiner rejected Claims 1-14 under 35 U.S.C. § 103 (a) as being unpatentable over U.S. Patent No. 5,961,952 ("Crane") in view of JP 11099192 ("Yamaguchi") and in further view of DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther").

The Board of Patent Appeals and Interferences ("Board") should reverse the Examiner's rejections since Crane in view of Yamaguchi and in further view of Schott

Glaswerke or Walther fails to disclose, teach, or suggest the present invention. Moreover, a proper combination of the references would, at best, teach away from the present invention.

A. The Examiner's Rejections of the Claims Should be Reversed Since Crane in view of Yamaguchi and in further view of Schott Glaswerke, or Walther does not disclose or suggest all the elements of claims 1-14 nor do these prior art references contain a motivation to combine one reference with the other reference.

The present invention is directed to a composition comprising a radiopharmaceutical in a container which has a silica coating on the inner surface where the improvement being that the radiopharmaceutical comprises a coordination complex of a metal with an organic ligand. The present invention also relates to kits for the preparation of sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface. Furthermore, Appellants position has consistently been that radiopharmaceuticals which are metal complexes (not 'metals') in such silica-coated containers are novel.

Crane simply discloses a method of using a metal complex and its analogs to diagnose or radioimage breast tumors. Crane only provides a vague reference to the use of a vial to hold its compounds. More importantly, Crane does not even disclose, teach, or suggest using any type of coating on the inner surface of the vial. Hence, the Appellants respectfully submit that Crane fails to provide any motivation for improving the vial, let along the inner surface for its compounds.

Yamaguchi discloses that silica-coated vials (prepared by a chemical coating and pyrolysis method), are useful to prevent adsorption of radiopharmaceutical products such as a thallium chloride, (^{201}Tl), solution to the surface of a glass. Yamaguchi provides no description of using metal complexes as radiopharmaceuticals. Furthermore, the present invention defines the term 'metal complex' as a coordination complex of a metal (M) with an organic ligand (L). This is to be contrasted with an uncomplexed or free metal ion such as the monovalent thallium cation, Tl^+, used in Yamaguchi.

Schott Glaswerke discloses that glass containers having an internal coating of SiO_2, prepared by a plasma chemical vapour deposition process, are useful for the storage of pharmaceutical or diagnostic solutions. However, Schott Glaswerke provides no further description of the contained material, other than the generic reference to 'pharmaceutical'. Schott is silent on radiopharmaceuticals, let alone radiopharmaceutical metal complexes,.

Walther discloses a glass tube with an oxide material preferably SiO_2, Al_2O_3, TiO_2 or mixtures thereof. Walther notes that the prior art taught a silica-coated tube for use with (generically) pharmaceuticals. Walther contains no reference to radiopharmaceutical metal complexes per se.

On page 4 of the Office Action dated December 12, 2007 ("Office Action") the Examiner states that "the claims [present claims 1-14] did not exclude radioactive thallium chloride, etc. complexes, neither did independent claim 1 require the presence of an organic ligand." Appellants respectfully submit that the Examiner's statement is inaccurate. The addition of a "metal" to the subject matter of Yamaguchi would not lead to the subject matter of present claim 1. Revised claim 1 makes it clear that an organic ligand which forms a

coordination complex with the radiometal (of the radiopharmaceutical) must also be present. It is clear that the chloride ion of Yamaguchi falls outside such a definition.

Appellants also disagree with the Examiner's construction. First, the Examiner's logic amounts to finding feature A in document 1 and feature B in document 2, and asserting that the combination is obvious. This approach would probably exclude from patentability all selection inventions or indeed claims in Jepson format. Appellants acknowledge that radiopharmaceuticals which are metal complexes are a subset of radiopharmaceuticals in general. Present claim 1 can therefore be regarded as a selection invention over Yamaguchi. That is the logic for the present two-part claim format. Selection inventions have long been regarded as patentable – as long as the subset/selection brings useful benefits that could not have been anticipated by the prior art. Appellants have argued at length that radiopharmaceuticals which are metal complexes suffer from a range of problems (not simply adsorption), which are solved by silica-coated containers. Yamaguchi teaches only solving adsorption problems for ionic radiopharmaceuticals (^{201}Tl as the Tl^+ cation), which are not metal complexes of organic ligands. These unforeseen problems, and their solution, were not contemplated by either Yamaguchi or Crane. The present selection invention is therefore believed to present a useful contribution to the art, and like other selection inventions should be patentable. Appellants refer to Crane – where ^{99m}Tc isonitrile complexes were known (see Crane Column 1 lines 15 – 26), and tumor imaging with such complexes was also known. A particular type of isonitrile complex (TBI) was, however, regarded as patentable since it had beneficial properties. If the Examiner's current approach and logic were applied, Crane could never have been granted.

Second, the Examiner's logic completely ignores the issues of the suitability of the combination, and motivation to combine. It simply asserts that if the two separate components/features are known in separate prior art documents, then the combination is always obvious. Is it the Examiner's position that 'motivation to combine' is irrelevant to an obviousness analysis? Certainly it would seem that Appellant's extensive arguments on the lack of motivation to combine in the present case have been repeatedly rejected – yet the Examiner has failed to produce any real argument for motivation.

Appellants point out that a proper analysis must be based on "knowledge which was within the level of ordinary skill at the time the claimed invention was made....". Appellants fail to see, however, that such a standard has been applied in this instance. The Examiner has disregarded all alternatives apart from those which lead to the subject matter of the present invention:

> (i) alternative coatings – the person skilled in the art had many coatings to chose from, all taught to have advantageous properties – such alternative coatings would include silicon-containing polymers such as silicones or silanes that are in regular use;
> (ii) features of Crane to improve – Crane teaches very many features, so the question why the vial/container was chosen is a real one; and
> (iii) removal of solubilizer – Crane teaches that a solubilizer is essential. The Examiner has consistently ignored Appellant's arguments that some additional teaching (or hindsight) would be necessary to justify this change. (please see page 10 of this appeal for further analysis).

The above mentioned are important illustrations of key questions facing the person skilled in the art at the time of the claimed invention. To date, the Examiner has failed to provide any argumentation on (iii), and very limited comments on (i) and (ii). Disregarding the many equally plausible alternatives of (i), and the many more plausible alternatives of (ii), and failing to address the incompatibility issues raised by (iii) is in Appellant's view evidence of a hindsight analysis. Consequently, Appellants contend that the Examiner has failed to provide a convincing argument as to motivation to combine based on the prior art of record. In the absence of such reasoning, Appellants maintain their position that an invalid hindsight analysis based on selection of features piecemeal has been applied by the Examiner.

Appellants also submit that the present invention describes at length how radiopharmaceuticals suffer from unforeseen or variable problems which are solved using silica-coated vials. See page 4, line 17 to page 9, line 23 of the present specification. None of these

problems were recognized in the prior art, and hence the cited references simply cannot provide a motivation to apply silica-coated vials to radiopharmaceutical metal complexes. The solution to the problem provided by the present claims is believed non-obvious for this reason.

Furthermore, the invention as taught by Crane at Columns 7 and 8 has many features: e.g.

tert-butyl Isonitrile ligand
^{99m}Tc or ^{186}Re/^{188}Re metal complex thereof
solubilization aid
reducing agent
pharmaceutically-acceptable carrier
a non-radioactive iso-butyl isonitrile metal complex precursor
pharmaceutically-acceptable filler
vial
lyophilization aids
buffers
stabilization aids
bacteriostats
transfer ligand,
etc.

Of all of these features, the Examiner has stated in previous Office Actions that it is the *vial* which the person skilled in the art would address to 'improve' on Crane. It is well settled that a reference must be considered not just for what it expressly teaches, but also for what it fairly suggests to one who is unaware of the claimed invention. *In re Baird*, 16 F.3d 380, (Fed. Cir. 1994). The Examiner's reasoning ignores the fact that Crane gives no description, at all, about the vial or indeed the inner surface wall of the vial but expounds at length about the

other features of the invention. In fact, Appellants respectfully submit, that Crane's inclusion of the vial is not a key contribution to the invention disclosed by Crane. The Examiner fails to demonstrate why one of ordinary skill in the art, upon reading Crane, would be motivated to select the vial – of all things – as the key to 'improving' Crane. Appellants contend that the Examiner has failed to show why the person skilled in the art would select only the vial from this long list of features to seek to improve, and as a consequence choose not to improve all the other aspects even those which Crane teaches as important. Furthermore, why would the person skilled in the art choose specifically silica-coated vials, when a great variety of alternative coatings (e.g. including silicon-containing polymers such as silicones or silanes) were available, in regular use, each also having "benefits"? In this respect the Appellants respectfully submit that the Examiner has failed to make a prima facie case of obviousness in rejecting the present invention.

Furthermore, a *prima facie* case of obviousness requires that motivation for the skilled artisan to modify or combine specific references exists. The Examiner's own statements [Office Action, October 26, 2004] refer to "various pharmaceuticals and/or radiopharmaceuticals" and "such as, those disclosed by Crane" and "reasonably pertinent to the problem being solved". These statements, however fail to address the key criterion of why the person skilled in the art would specifically choose Crane to combine with, and hence where the clear motivation exists to apply, the silica-coated containers to radiopharmaceutical metal complexes. It is not clear exactly what the specific "benefits" expected for radiopharmaceutical metal complexes would be. The Examiner's own statements seem to suggest that the person skilled in the art *could* apply the silica-coated vials to *any* radiopharmaceutical, of which Crane

is merely illustrative. However, to state that one 'could' combine references is not the standard for making a prima facie case of obviousness as such a standard would only grant patentability to combinations which 'could not' be made. Indeed, if the Examiner's logic was followed, then all radiopharmaceuticals would be provided in silica-coated vials, once the cited prior art in question had published, and no one would contemplate using uncoated vials, since it would be folly to ignore the purported 'benefits'. In reality, uncoated vials are still very much the norm for radiopharmaceuticals and coated vials (in any form), the exception. This is because coated vials are significantly more expensive, and no one would accept the additional costs for unspecified "benefits" that were not clearly identified as necessary for the specific product. Accordingly, Appellants respectfully disagree with the Examiner's basis for finding a motivation to combine references.

The Examiner argues that the person skilled in the art would be motivated to combine Crane and Yamaguchi to solve absorption problems. Crane, however, specifically teaches "solubilization aids" as an essential feature to solve this problem described therein:

Column 2 lines 33-47 and 56-57,
Column 3 lines 23-33 and 46-47,
Column 7 lines 1-26.

The logic of the Examiner's combination is that the 'solubilization aid' taught by Crane would no longer be necessary, since the coated vial would (presumably) solve the absorption problem. This contradicts the teaching of Crane, in that the absence of the 'solubilization aid' would remove an essential teaching of Crane. Accordingly, combining Crane and JP '192 in this manner is an invalid combination.

Additionally, even assuming, *arguendo*, that the references are properly combinable; Appellants respectfully submit that any such combination would teach away from the present invention. 'Teaching away' simply means teaching a solution that would not lead to the claimed subject matter. As noted by the Federal Circuit:

> A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. (emphasis added).
>
> *Para-Ordnance Mfg. v. SGS Importers Int'l*, 73 F.3d 1085 (Fed. Cir. 1995).

Appellants respectfully submit that the mere fact that a reference may suggest an 'improvement' does not dictate that the improvement will direct one to all other 'improvements'. That is, one improvement can teach away from another, as the two improvements may diverge from each other in their teachings. The *Para-Ordnance* decision (above) clearly states that teaching away does not require a negative teaching in the prior art, the prior art need only teach other, divergent, solutions to be deemed to teach away from an invention.

Thus, by teaching positively towards certain embodiments or features as being important or preferred, the art provides a motivation for the person skilled in the art to go in a particular direction. If that direction leads towards subject matter outside the scope of the claims at issue, then it constitutes a "teaching away". Appellants maintain that the person skilled in the art, even if assumed to be contemplating improvements of Crane, would focus on the specific teachings in Crane of embodiments taught to be important, and be motivated to improve those elements. Crane teaches that a method of using a metal complex and its analogs to diagnose or

radioimage breast tumors to be important. Again, per *Baird*, it is well settled that a reference must be considered not just for what it expressly teaches, but also for what it fairly suggests to one who is unaware of the claimed invention. *In re Baird supra*. Crane is clearly directed to the use of radiopharmaceutical metal complexes as breast tumor diagnosing or imaging agents, which is described at length from Column 2 line 7 to Column 5 line 21. That is, Crane devotes about four columns of text to what is the essence of his invention, the metal complexes, and not to containers for those metal complexes. Again, Crane itself does not discuss the features of the containers used for the compounds, and hence gives no weight to that feature. Crane's emphasis on using metal complexes as breast tumor diagnosing or imaging agents, and the apparent satisfaction with the conventional (ie. uncoated) vial would indicate that improvements to the metal complexes as breast tumor diagnosing or imaging agents are found by adjusting the formulation of the metal complexes and/or diagnosing or imaging agents, not by modifying the vial.

Accordingly, as none of the cited references are properly combinable so as to render the present invention obvious, Appellants respectfully request that the Board reverse the Examiner's rejections and direct that claims 1-14 be allowed.

Unlike Crane in view of Yamaguchi and further in view of Schott Glaswerke or Walther, claim 1 teaches an improvement of a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface. Crane does not even disclose, teach, or suggest using a composition in combination with a coating on the inner surface of the vial. Additionally, Yamaguchi provides no description of using metal

complexes as radiopharmaceuticals nor does it disclose, teach, or suggest preparing the silica-coated vials by a plasma chemical vapour deposition (PCVD) process. Furthermore, Schott Glaswerke provides no further description of a contained material, other than the generic reference to 'pharmaceutical'. Schott is silent on radiopharmaceuticals, let alone radiopharmaceutical metal complexes. Likewise, Walther notes that the prior art teaches a silica-coated tube that can be used with generic pharmaceuticals but does not disclose, teach, or suggest any reference to radiopharmaceutical metal complexes let along the combination of using silica-coated tubes with radiopharmaceutical metal complexes.

In another light, claim 6 teaches the use of a kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica-coated inner surface. Crane in view of Yamaguchi, and further in view of Schott Glaswerke or Walther do not even disclose, teach, or suggest using a non-radioactive kit provided in a vial having a coating on the inner surface, for the preparation of a radiopharmaceutical metal complex.

Additional claim 10 further teaches another use for a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface. Claim 10 discloses a composition for the preparation of a stabilized radiopharmaceutical metal complex which comprises a stabilizer capable of stabilizing said radiopharmaceutical metal complex and an organic ligand which forms a coordination complex with the metal in a container which has a silica coating on the inner surface. Crane in view of Yamaguchi and in further view of Scott

Glaswerke or Walther do not even disclose, teach, or suggest using the present invention composition claim 10.

Finally, claim 11 teaches yet another use of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface. Crane in view of Yamaguchi and further in view of Schott Glaswerke or Walther do not even disclose, teach, or suggest using the present invention composition claim 11.

Accordingly, Appellants respectfully submit that the instant application, including claims 1-14, is in condition for allowance. Favorable action thereon is respectfully requested.

Conclusion

In view of the foregoing, Appellants respectfully request that the Board reverse the rejections of Claims 1-14 as set forth in the Office Action mailed December 12, 2007, that the Board allow the pending claims since they are in condition for allowance, and that the Board grant any other relief as it deems proper.

Dated: May 9, 2008

Respectfully submitted,

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XIII. CLAIMS APPENDIX

1. In a composition which comprises a radiopharmaceutical in a container which has a silica coating on the inner surface, the improvement being that the radiopharmaceutical comprises a coordination complex of a metal with an organic ligand.

2. The composition of claim 1 wherein the radiopharmaceutical is a liquid or solution.

3. The composition of claim 1 wherein the metal of the metal complex is ^{111}In or ^{99m}Tc.

4. The composition of claim 1 wherein the silica coating is deposited by a PCVD process.

5. The composition of claim 1 wherein the container is a glass vial with a closure.

6. A kit for the preparation of a sterile radiopharmaceutical metal complex which comprises a non-radioactive organic ligand composition in a container which has a silica coating on the inner surface.

7. The kit of claim 6 wherein the metal complex is a ^{99m}Tc complex.

8. The kit of claim 6 wherein the non-radioactive organic ligand composition is lyophilized.

9. The kit of claim 6 wherein the silica coating is deposited by a PCVD process.

10. A composition for the preparation of a stabilized radiopharmaceutical metal complex which comprises (i) a stabilizer capable of stabilizing said radiopharmaceutical metal

complex; and (ii) an organic ligand which forms a coordination complex with the metal; in a container which has a silica coating on the inner surface.

11. A composition for the preparation of a sterile radiopharmaceutical metal complex which comprises a bacteriostat suitable for use with a radiopharmaceutical metal complex in a container which has a silica coating on the inner surface.

12. The composition of claim 11, wherein the bacteriostat comprises a paraben.

13. The composition of claim 10 wherein the metal of the metal complex is ^{111}In or ^{99m}Tc.

14. The composition of claim 10 wherein the silica coating is deposited by a PCVD process.

IX. EVIDENCE APPENDIX

Appellants hereby append copies of the following patents:

U.S. Patent 5,961,952 by Crane;

English translation of Japanese Patent JP11099192;

English translation of German Patent DE29609958 by Schott Glaswerke; and

U.S. Patent 6,200,658 by Walther.

This is the evidence relied upon by the Examiner for rejection of appealed Claims 1-14 in the Office Action dated December 12, 2007.

X. RELATED PROCEEDINGS APPENDIX

There are no other appeals or interferences related to the instant appeal.